UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,113	02/28/2006	Mariagrazia Pizza	PAT051720-US-PCT	8533

27476 7590 11/12/2009

NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY- X100B
P.O. BOX 8097
Emeryville, CA 94662-8097

EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
11/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,113	PIZZA ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-19* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2009 has been entered.

Applicant's supplemental response filed on August 31, 2009 is acknowledged. Claims 1-8 and 11-19 are pending. Claim 1 has been amended. Claims 13-18 were previously withdrawn. Claims 1-8, 11, 12 and 19 are under examination.

Information Disclosure Statement

2. Applicant is reminded that the listing of references in the specification at pages 12-15 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Moreover, Applicant must comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to

be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Rejections Withdrawn

3. In view of Applicant's argument, the rejection of claims 1-8, 11, 12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (Analytical Biochemistry, 1994; 216: 47-51) and van der Ley et al. (Vaccine; 1995; 13(4): 401-407) is withdrawn.

4. In view of Applicant's argument, the rejection of claims 1, 2, 11, 12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (U.S. Patent 7,081,244 B2) in view of van der Ley et al. (Vaccine; 1995; 13(4): 401-407) is withdrawn.

New Grounds of Objection/Rejection

Claim Objections

5. Claim 12 is objected to because of the following informalities: on first sight the acronym "OMV" should be followed by "Outer Membrane Vesicle". It is suggested that the abbreviation be defined in claim 1, for example, outer membrane vesicle (OMV). Appropriate correction is required.

Drawings

6. The drawings are objected to because Figure 3 contains sequences that have not been identified by sequence identifiers (i.e. SEQ ID NO) in the drawings or in the Brief Description of the Drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 5-7, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Gorringe et al. (WO 01/73080 A2).

The rejected claims are drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA (see page 5, lines 26 and 35). Gorringe et al. disclose that the invention provides a cell expressing Neisserial transferring binding protein (Tbp), wherein the Tbp can be extracted from the cell under mild conditions. Gorringe et al. disclose that the invention is an application for the overexpression of Tbps in organisms that are known to express Tbps. The invention is designed to use commensal Neisseria expressing an iron uptake

protein from a pathogenic Neisseria, particularly one expressing TbpA, such as *N. meningitidis* strain K454, which is a serogroup B bacterium (see page 4, lines 4, 5 and 12-14; page 7, lines 16-20). Gorringe et al. disclose that the Tbp is extracted by solubilising the membrane associated with Tbp in a non-ionic detergent solution (see page 6, lines 1 and 2), thus meeting the limitation "in the absence of deoxycholate detergent". Moreover, Gorringe et al. disclose that crude membranes were prepared by disrupting cells with a bead-beater (the Examiner has interpreted this to meet the limitation of "wherein the bacterial membrane is disrupted substantially in the absence of any detergent). The cell suspension was transferred to a vessel half filled with 0.25-0.5mm diameter glass beads. The vessel was sealed and placed on to the bead-beating apparatus. The suspension was beaten for 15 seconds to disrupt the cells. Once the beads had settled the suspension was decanted off and centrifuged at 8000g for 30 min. The supernatant was discarded and the pellet containing crude membranes was resuspended in the original volume of 100 mM Tris-HCl buffer, pH 8,0, containing 0.5M NaCl. Once an even suspension was obtained an equal volume of Tris-HCl buffer, pH 8.0, containing 0.5M NaCl and 4% (v/v) Elugent ™ detergent was added. The suspension was incubated with gentle stirring at 4°C for 16 h. The suspension was then centrifuged at 39000g for 10 mi and the supernatant containing soluble rTbps was decanted off (see page 12, lines 25-37 and page 13, lines 1-2; extraction from membrane preparations). Lastly, Gorringe et al. disclose that the composition can be included in vaccine compositions (see abstract).

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-8, 11,12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (Analytical Biochemistry, 1994; 216: 47-51) in view of Gorringe et al. (WO 01/73080 A2) as applied to claims 1-3, 5-7, 11 and 12 above, and van der Ley et al. (Vaccine; 1995; 13(4): 401-407) and further in view of Rosenqvist et al. (WO 01/91788 A1).

The rejected claims are drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

Morein et al. disclose a rapid and simple method of preparing outer membrane vesicles from a Gram negative bacterium. The process includes lysing the bacteria to prepare membrane vesicles. Morein et al. disclose that the cells were either passed through a French pressure cell or converted to spheroplast and briefly sonicated (see page 48; Preparation of Membrane Vesicles; 1st paragraph). Morein et al. disclose that after lysis of the bacteria, unlysed cells were sedimented by a low-speed centrifugation at $1500g_{max}$ for 15 minutes. The membrane vesicles from the supernatant were collected by a centrifugation at $257,000g_{max}$ for 90 min at 4°C in a Ti70 rotor with a Beckman ultracentrifuge. Moreover, Morein et al. disclose that it is possible to dilute the supernatant from the low-speed centrifugation step with a buffer, mix it with Percoll and perform the density gradient centrifugation (see page 48; Preparation of Membrane Vesicles; 4th paragraph). Morein et al. disclose that the membrane pellet was suspended in a small volume buffer C, which included tris-HCL. The membrane mixture was mixed and then centrifuged (see page 48; Gradient Centrifugation; 1st paragraph). Morein et al. disclose that the supernatant from the low-speed centrifugation containing the membrane vesicles was directly diluted with buffer C, mixed with Percoll to a concentration of 16.2% by volume and centrifuged (see page 48; Gradient Centrifugation; 2nd paragraph).

Morein et al. do not specifically disclose that the outer membrane vesicle preparation is from *N. meningitidis* strain H44/76 or *N. gonorrhoeae* and over-expresses TbpA; they do not disclose that the process comprises sterile filtration through at least

two filters of decreasing pore size of the re-dispersed composition or that the pore size is about 0.2 μm.

Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA (see page 5, lines 26 and 35). Gorringe et al. disclose that the invention provides a cell expressing Neisserial transferring binding protein (Tbp), wherein the Tbp can be extracted from the cell under mild conditions. Gorringe et al. disclose that the invention is an application for the overexpression of Tbps in organisms that are known to express Tbps. The invention is designed to use commensal Neisseria expressing an iron uptake protein from a pathogenic Neisseria, particularly one expressing TbpA (claim 1), such as *N. meningitidis* strain K454, which is a serogroup B bacterium (claim 11) (see page 4, lines 4, 5 and 12-14; page 7, lines 16-20). Gorringe et al. disclose that the Tbp is extracted by solubilising the membrane associated with Tbp in a non-ionic detergent solution (see page 6, lines 1 and 2), thus meeting the limitation "in the absence of deoxycholate detergent". Moreover, Gorringe et al. disclose that crude membranes were prepared by disrupting cells with a bead-beater (the Examiner has interpreted this to meet the limitation of "wherein the bacterial membrane is disrupted substantially in the absence of any detergent). The cell suspension was transferred to a vessel half filled with 0.25-0.5mm diameter glass beads. The vessel was sealed and placed on to the bead-beating apparatus. The suspension was beaten for 15 seconds to disrupt the cells. Once the beads had settled the suspension was decanted off and centrifuged at 8000g for 30 min. The supernatant was discarded and the pellet containing crude

membranes was resuspended in the original volume of 100 mM Tris-HCl buffer, pH 8,0, containing 0.5M NaCl. Once an even suspension was obtained an equal volume of Tris-HCl buffer, pH 8.0, containing 0.5M NaCl and 4% (v/v) Elugent ™ detergent was added. The suspension was incubated with gentle stirring at 4°C for 16 h. The suspension was then centrifuged at 39000g for 10 mi and the supernatant containing soluble rTbps was decanted off (see page 12, lines 25-37 and page 13, lines 1-2; extraction from membrane preparations). Gorringe et al. disclose that the composition can be included in vaccine compositions (see abstract).

van der Ley et al. disclose the use of *Neisseria meningitidis* strain H44/76 (claim 19) for the production of an outer membrane vesicle vaccine.

Rosenqvist et al. disclose a process for the production of outer membrane vesicle vaccines. Rosenqvist et al. disclose that sterile filtration of purified OMV is accomplished by using a series of three separate filters with decreasing pore sizes (claim 4) (see page 20, lines 1-12). Moreover, Rosenqvist et al. disclose the use of 0.2 µm filters (claim 8) (see page 20, line 30).

Morein et al. , Gorringe et al., van der Ley et al., and Rosenqvist et al. disclose analogous inventions related to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, it would have been prima facia obvious at the time the invention was made to use Neisseria bacterium that over-expresses TbpA because meningococcal infections are increasing and the meningococcal transferring receptor is a suitable vaccine component made up of transferring binding protein A (TbpA) and B (TbpB), consequently producing outer membrane vesicle membranes that over-express

TbpA provides an alternative and/or improved recombinant production of TbpA (see Gorringe et al.; page 1, lines 14-16 and page 2, lines 33-38).

It would have been prima facia obvious at the time the invention was made to use *N. meningitidis* strain H44/76, which is from serogroup B because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Moreover, it would have been obvious at the time the invention was made to perform sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition from step (f) because a smaller size filter, particularly a 0.2 μm filter yields vesicles with less rupture and damage (see Rosenqvist; page 21, line 1) and because the known technique was recognized as part of the ordinary capabilities of one skilled in the art.

It would have been expected, barring evidence to the contrary, that the strain together with the process steps would be effective for the manufacturing of an outer membrane vesicle. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396). By all comparative data the method of the prior art and the instantly claimed method absent evidence to the contrary are one in the same.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
11/2/09

/Vanessa L. Ford/

Primary Examiner, Art Unit 1645